Scope of Regulatory Approach for Cellular Therapies Under 21 CFR Part 1271

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Focus

- Background/scope
  - Identified need for new approach to regulation
  - 1997 Proposed Approach
  - 1998 FR Notice: Stem Cell Standards
  - 21 CFR Part 1271 regulation development
- Registration and listing final rule
  - Registration specifics/scope
  - Criteria for regulation as 361 vs. 351
  - Current status

Why New Requirements for Cells/Tissues?

- Rapidly growing industry
- New techniques for processing and manipulating human cells and tissue
- Promise of hematopoietic stem cells for hematopoietic reconstitution
- Increasing international commerce
- Increasing public health concern with transmission of communicable diseases

Why New Requirements for Cells/Tissues?

- Emerging disease agents pose potential threats
- Public expectation for safety is high
- Industry standards not always followed and are unenforceable
- Demand for tissue/cell products likely to increase
- Perception of poorly regulated industry could thwart tremendous technological promise

Why New Approach?

- Fragmented regulation of tissues/cells
- Some actively regulated while others not
- Opportunity to develop new risk-based framework
  - Address hematopoietic stem cells
  - Positive feedback from industry, academia, consumer groups
  - Relied on existing laws
  - Excluded products, e.g., organs, blood and xeno products, minimally manipulated bone marrow

1997 Proposed Approach

- Tiered level of regulation -risk based
- Focus on preventing transmission of communicable disease
- Safe processing and handling
- Clinical safety and effectiveness addressed where appropriate
- Broad range of products
- Implemented by rule-making
- Allowed for public comment

1998 Request for Proposed Standards

- Focused on unrelated allogeneic peripheral and placental/umbilical cord blood hematopoietic stem/progenitor cell products – 351 HCT/Ps
- Requested submission of
  - Proposed product standards
  - Proposed establishment and processing controls
  - Supporting clinical and nonclinical laboratory data
  - Other relevant information related to ensuing safety and effectiveness
  - These HCT/Ps are currently in an IND moratorium
- FDA would review and assess the information submitted
- Determine regulatory approach to licensure - in progress

Public Meetings Since 1997

- September 1998 FDA/NHLBI workshop
  - Peripheral and cord blood stem cells
  - Request for standards
  - Status of professional voluntary standards development
  - Collection and transplantation data
- August 2000 FDA/NHLBI workshop
  - Cord blood
- February 2003, Biological Response Modifiers Advisory Committee
  - Cord blood

21 CFR Part 1271
Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

Regulation Subparts	Proposed	Final	Effective Date
Establishment Registration and Product Listing	1998	2001	2001 for establishments regulated under 1270 2004 for newly regulated establishments
Donor Eligibility	1999	2004	May 25, 2005
Current Good Tissue Practices: Inspection and Enforcement	2001	2004	May 25, 2005

Guidance

- Draft – Preventive Measures to Reduce the Possible Risk of Transmission of CJD/vCJD by HCT/Ps - June 2002
- Draft – Eligibility Determination for Donors of HCT/Ps - May 2004
- Final - donor eligibility guidance will combine the above drafts –FDA addressing comments to the docket now
- GTP guidance – currently leveraging with industry professional associations to develop draft guidance

Final Rule: Registration and Listing

- Subpart A and B of 21 CFR Part 1271
- Provides purpose and scope for all parts of the regulation
- Important definitions
- Criteria that need to be met to be regulated solely under section 361 **(**without pre-market approval**)**
- Six Exceptions from registration
- Procedures for registration and listing
- All establishments should have registered by January 2004

Registration and Listing

- Required for establishments that engage in the manufacture of HCT/Ps
- Manufacture includes recovery, processing, storage, labeling, packaging, or distribution of a HCT/P or screen or test the donor
- Exemption for establishments that do not manufacture, but only receive or store for use in the establishment – ex., hospitals, transfusion centers

Conforming Amendments

- Modified 207.20 registration and listing for producers of drugs and listing of drugs in commercial distribution
- Modified 807.20 registration and listing for manufacturers and distributors of devices
- If the establishment manufactures an HCT/P considered a drug (biologic) or device, they must now follow the 1271 procedures for registration and listing

Registration Continued

- Establishments previously listing hematopoietic stem cells as a blood product must now register and list per 1271
  - 86 blood registrations identified and notification letters sent
- Registration does not constitute a determination that an establishment is in compliance with the regulations –this is determined during a facility inspection

International Establishment Registrations

- Required if distributing HCT/Ps in the US
- Need to identify a US based agent
  - Provide address and phone number
  - Foreign establishment is not required to notify their US agent when shipping products
- Responsibilities of US agent include assisting FDA with communications concerning products and in scheduling inspections
- Future compliance with Bioterrorism Act – may require electronic listing of all consignees

Who Should/Should Not Register

- **Yes**-test lab that performs donor testing for communicable diseases
  - Don't need to list tissues – just check function
- **Yes**-establishments that process, store and/or distribute 361 or 351 licensed cell therapies
- **Yes**-test lab that performs microbiological testing of donor tissue
  - Now considered processing
- **No**-transfusion service that stores only for use in their facility

1271.10 Criteria for Regulation Solely under Section 361

- **All 4 criteria must apply** – if an HCT/P does not fit all, then it is regulated as a biological product or medical device:
- Minimal manipulation
- Homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent
- Not combined with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent that do not raise new clinical safety concerns with respect to the HCT/P and

1271.10 Continued

- Either:
- Does not have a systemic effect and is not dependent on the metabolic activity or:
- Has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and
  - Is for autologous use;
  - Is for allogeneic use in a 1st or 2nd degree blood relative or
  - Is for reproductive use

Definitions

- **Minimal Manipulation** means:
  - For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement; and
  - For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.
- **Homologous use** means the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor.

1271.20 - HCT/Ps That Don't Fit!

- If an HCT/P does not meet the 4 criteria for regulation under section 361 of the PHS Act
- Then it is regulated as a drug, device, and/or biological product (ex. Carticel, unrelated allogeneic, minimally manipulated hematopoietic stem cells)
- Requires pre-market approval – licensed, approved or cleared
- No registration/listing is required until the HCT/P is licensed, approved or cleared for marketing

What Does This Mean for Cell Therapies?

- 361 Regulated
  - Autologous or family related and
  - Minimally manipulated and for homologous use, and
  - Not combined with another article
- 351 Regulated
  - All unrelated allogeneic
  - Some autologous or family related if more than minimally manipulated, for non-homologous use or combined with another article

Registration Current Status

- Human Cells and Tissues Establishment Registration (HCTERs) Database
- 1601 establishments currently actively registered
  - 651 Musculo-skeletal, ocular, skin
  - 485 Hematopoietic stem cells
    - 428 Peripheral blood
    - 169 Umbilical cord blood
    - 139 Donor leukocytes for infusion
  - 449 Reproductive tissues/cells
  - 20 Somatic cells –most voluntary
- Includes 153 foreign establishments – mostly list only hematopoietic stem cells

Scope of Investigational Cell Therapies: 351 HCT/Ps

- 362 IND/IDE's
  - 114 Peripheral blood stem cells
    - 65 IND's
    - 49 IDE's – based on cell selection device
  - 19 umbilical cord stem cell IND's
  - 3 donor lymphocyte for infusion IND's
  - Majority of others - somatic cell therapies
- Wide range of indications, e.g.,
  - Hematopoietic reconstitution
  - Disease treatments – malignant and non
  - Graft vs. host
  - Immunotherapy
  - Induction of tolerance
  - Myocardial infarction

Summary

- Review your Form 3356 registration form
  - 361 vs. 351 – is this accurate?
  - Micro testing on HCT/P
    - In house - check “process” box
    - Outside lab – don’t check, but determine that they are registered
  - Communicable disease donor testing
    - In house – check “test” box
    - Outside lab - don’t check, but determine that they are registered
  - Submit annually- new signature/date
- 1271 effective for HCT/Ps recovered on or after May 25, 2005
- Call FDA if you think you have a HCT/P that should be under IND or IDE – 301-827-6536
- If other questions, wells@cber.fda.gov, 301-827-6106

Thank You